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Endplate defect is heritable, associated with low back pain and triggers intervertebral disc degeneration: a longitudinal study from TwinsUK

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ABSTRACT

Study design: Longitudinal study of spine magnetic resonance imaging (MRI) in a large-scale population-based study.

Objective: To determine the order of appearance of degenerative change in vertebral bodies and intervertebral discs. We also sought to define the influence of endplate defect on low back pain (LBP) and to determine whether there is a genetic influence on endplate defect.

Summary of background data: Endplate defect is a magnetic resonance imaging trait, found to be associated with intervertebral disc degeneration. There is a lack of understanding regarding the mechanism underlying lumbar disc degeneration (LDD). Recent attention has shifted to vertebral endplate defects and their role in spine degeneration pathology.

Methods: Individuals from the TwinsUK spine study having longitudinal T2-weighted lumbar MR scans at baseline (n=996) and a decade later (n=438) were included. LDD, vertebral endplate defect by calculating a total endplate (TEP) score and Modic change (MC) were assessed using standard techniques. Mixed-effects models were used to determine the

association between the features of spine pathology, adjusted for covariates. Endplate defect heritability was estimated using variance component analysis.

Results: Significant association was found between endplate defect, LDD, MRI features of LDD and MC was observed. Endplate defect was associated with severe disabling LBP ($p=0.013$) in multivariate analysis. An association between disc degeneration (DD) at baseline and MC at follow-up was shown at upper lumbar levels. TEP score was heritable with estimated additive genetic component $A = 55.3\%$ (95% CI 43.0-65.4).

Conclusion: Endplate defect, LDD and MC are all independent risk factors for episodes of severe and disabling LBP. Longitudinal analysis showed DD is followed by MC. Endplate defect has significant heritability of 55%. However, whether endplate defect triggers DD or these pathological changes occur concurrently could not be conclusively determined.

KEY WORDS

Endplate, intervertebral disc, disc degeneration, Modic change, lumbar spine, magnetic resonance imaging, Pfirrmann, total endplate score, twin, heritability, lower back pain, TwinsUK

Level of evidence: 2

KEY POINTS

- Endplate defect is a magnetic resonance imaging trait, found to be associated with intervertebral disc degeneration.
- Total endplate score (TEPS) was based on endplate defects, an overall size index of Modic change was calculated and a segmental sum for each lumbar level and disc degeneration was evaluated using two different classifications (Pfarrmann and 4-point grading system).
- This is the first study to report an estimated heritability (55%) for endplate defect in the lumbar spine.
- Furthermore, we propose sequence of pathological changes in disc degeneration, through longitudinal analysis in a large population based sample.

MINI-ABSTRACT

This large longitudinal study from TwinsUK showed that disc degeneration is followed by Modic change in the lumbar spine and lumbar vertebral endplate defect has significant heritability of 55%.

INTRODUCTION

Low back pain (LBP) is a highly prevalent musculoskeletal condition and a major cause of disability activity limitation and work absence globally. Intervertebral disc degeneration (DD) in the lumbar spine (LDD) is a major risk factor for episodes of severe and disabling LBP in the general population (1). LDD is a multifactorial condition, with risk factors including age, sex, obesity and smoking. LDD is highly heritable (34%-76%) (2, 3), but many of the genetic factors predisposing to this condition remain to be determined.

Modic change (MC) describes lesions within the bone marrow of vertebrae adjacent to the vertebral endplates (4). Originally, MCs were classified into subtypes, characterised by the intensity of signals on T1W and T2W images. MC has been widely associated with LDD both in patients and in population samples (5, 6). MC is also heritable, with estimates of 30% (95% CI:16-43) in the TwinsUK cohort (6).

The vertebral endplate experiences significant mechanical pressure and distortion through daily activities making it prone to failure and degeneration (7). The double-layer of the endplate (cartilaginous and bone) is thought to provide an optimal balance between the transport of solutes to meet the metabolic demands of disc cells facilitated by a more porous cartilage layer and strength to resist mechanical failure by a thicker, denser bony layer. Endplate defect has been associated with LDD and severe disabling back pain (8), but the association between MC and endplate defect has not been extensively evaluated and the genetic influence on intervertebral endplate has yet to be studied.

The objective of this study was to determine the temporal sequence of LDD associated features (endplate defect, MC and LDD) in spine degeneration pathology and to estimate the heritability of endplate defect.

PATIENTS AND METHODS

Subjects for this study were twins enrolled in the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) BioResource TwinsUK adult twin registry based at King's College London (9). For historic reasons, most twin volunteers are female and have been shown representative of the general singleton population (10). Between 1996 and 2000 unselected twin pairs were invited to attend a clinic where a T2 weighted sagittal lumbar MRI scan would be performed, a nurse-led interview (2). 996 twins attended at this time-point. The twins were neither selected nor excluded for LBP. Episodes of severe disabling LBP of duration of more than one month at any point in an individual's total lifetime history were evaluated using a modified version of the MRC Back and Neck Pain Questionnaire, a standardised questionnaire (1). Zygosity was determined using a standard questionnaire and where there was uncertainty, confirmed by multiplex DNA fingerprint testing.

The twins included in the baseline study were re-contacted a decade later and for funding reasons half the pairs (450 twins) re-attended for a clinical visit and repeat T2 weighted lumbar MRI scans. Ethics permission was obtained (St Thomas' Hospital ethics committee, the tenets of the Declaration of Helsinki were adhered to and written informed consent was obtained. Baseline MR T2 weighted sagittal imaging was performed using a Siemens (Munich, Germany) 1.0T superconducting magnet and follow-up scans using a 1.5T magnet, as previously reported (2, 11).

Evaluation of endplate defect

Vertebral endplates were classified and scored into six types, as per the classification Rajasekaran et al. (2008) (12). Rostral and caudal endplates were coded using middle sagittal slices at each lumbar segment for all baseline, and follow-up MRI scans, with no prior clinical knowledge of clinical status, scan sequence or subject details. Rostral and caudal endplate scores were summed to generate a total endplate (TEP) score for each lumbar level (13). Inter-rater agreement for the coding of endplate defect was calculated using Cohen's weighted kappa and Pearson's correlation. An initial training phase was held in which an inter-rater agreement on endplate defect detection and grading of ≥ 0.85 was reached on at least 100 subjects and 1000 endplates. After the training phase, potential uncertainties were settled by discussion and consensus. Weighted Cohen's kappa showed inter-observer reliability ranged from 0.80 - 0.88, depending on the vertebral endplate at baseline. At baseline and follow-up, the intra-observer reliability ranged from 0.77 - 0.97, depending on the vertebral endplate.

Evaluation of Modic change

MC was defined as the presence of high or low signal at the vertebral body levels L1-S1. The presence and size of MC had previously been recorded without specifying the subtype, for all baseline and follow-up scans (6). Rostral and caudal endplates were coded at each lumbar segment, using the same quantitative coding method. The overall size index of MC was calculated and a segmental sum calculated for each lumbar level.

Evaluation of disc degeneration

LDD had been scored using 4-point grading system. In the 4-point grading system disc signal, disc bulge, disc height loss and anterior osteophytes were coded 0-3 from the atlas, using the middle slice MR image, as described previously (2, 13, 14). Disc degeneration summary score was calculated by summing scores for the four traits at each of the five lumbar levels. DD had also been evaluated using the Pfirrmann classification, a progressive grading system from I to V (15). A previous study examining LDD reported that grade IV and V discs were regarded as degenerate (12).

Statistical analyses

Generalised linear mixed-effects models were used to assess risk factors for LBP, MC and LDD summary scores and to determine the order of pathological events adjusting for age, sex, BMI and family structure (twin relationship). Ordinal mixed-effects models were used to assess risk factors for LDD adjusting for covariates. Only participants with complete data were included in regression models. All statistical analyses were performed in RStudio, Version 1.0.136. Heritability estimates were calculated using structural equation modelling using OpenMx package for R (16).

RESULTS

Complete MRI data were available for 996 twins at baseline and 414 at follow-up. The majority of the sample was female (96.1%) (Table 1), with mean age =53.6 years (range 19.0-73.8), Mean BMI = 25.0 (range 16.2-51.4) Kgm-2. The lifetime prevalence of an episode

of disabling LBP of a duration longer than 1 month was 23.4%, with rates of 26.5% and 22.2% in MZ and DZ respectively.

Endplate score

The mean TEP score at baseline rose progressively higher going down the lumbar spine, range 4.58 at L1-2 to 5.46 at L5-S1 (Supplementary 1). At follow-up, the mean TEP score = 5.70 at L1-2 and 7.82 at L5-S1. At most lumbar levels endplate score was higher at caudal endplates – both at baseline and follow-up. TEP was seen to progress over time, with a statistically significant lower score observed at baseline compared to follow up ($p < 0.001$) at each lumbar level. Endplate defect progression was observed in over half of the subjects, with the highest rates of progression at L3-4 of 65.2%. Endplate defect regression (improvement) was also documented in a small proportion of the sample, highest rate L1-2 = 9.90%. Overall, a highly statistically significant deterioration was seen for TEP score at all individual lumbar levels ($p < 10^{-6}$) at every lumbar level over the decade of follow-up.

Association between endplate defect and severe disabling back pain

Considering severe and disabling LBP at baseline, we found a significant association between TEP score and severe disabling LBP ($p = 0.013$) at every lumbar level even after adjustment for risk factors age, sex and BMI ($n=820$, subjects Table 2).

Association between endplate change and lumbar disc degeneration

Risk factors for change in DD graded using the 4-point grading classification were assessed in 391 twins. Change in TEP score was found to be significantly associated with changes in DD at all lumbar levels (Supplementary 2) suggesting a tight relationship between endplate and disc degenerative processes, even in this smaller subset over just 10 years. Findings were similar when the Pfirrmann score was used rather than the 4-subtrait summary score (Supplementary 3).

Association of endplate change with Modic change

The presence and size of MC for baseline and follow-up as well as covariates was available for 410 twins, with changes in TEP score between baseline and follow-up significantly associated with change in MC size at all lumbar levels ($p < 2e^{-4}$) (see Supplementary 4).

Order of pathological change

Regression analysis was used to determine the relationship between endplate defect (TEP score), LDD (Pfirrmann score ≥ 4) and MC. All possible pairwise relationships of MC, endplate defect and DD were tested (Table 3). Only females were included with adjustment for age, BMI and family structure. Association testing showed that DD leads to MC at upper levels but at L5-S1 MC precedes DD. While association between baseline endplate defect and DD at follow-up as well as baseline DD and endplate defect at follow-up could be demonstrated, it cannot be conclusively determined the order of these pathological changes at the upper lumbar levels.

Heritability of endplate defect

Heritability estimates were calculated for normalised TEP score adjusted for age, sex and BMI. Only paired twins were included (379 twin pairs). The full model (ACE) fitted the observed phenotypic variance based on maximum likelihood estimation. Model fit for the full ACE model was evaluated using Chi-squared statistic and compared to that of nested models (CE, AE, E) under the principle of parsimony. The AE model provided the best balance between model fit and parsimony and this AE model gives additive genetic effects (A) = 55.3% (43.0%-65.4%) of TEP score variance.

DISCUSSION

LDD is a major risk factor for episodes of LBP (1). The precise aetiology of LDD is variable; recently it has been proposed to subdivide LDD into two distinct phenotypes: endplate driven DD and annulus driven DD (3, 17). Endplate driven LDD has been associated with endplate defect, most prevalent in thoracic and upper lumbar spine (3,18). In contrast, annulus driven LDD, associated with annulus fissures (and lower heritability) occurs primarily in the lower lumbar spine (L4-5 and L5-S1).

The present study in a large sample provides clear evidence that endplate change is an independent risk factor for severe and disabling LBP in a volunteer sample of general population. This illustrates that endplate defect has a role in LBP in the general population, at least in women, and is in accord with findings from small clinical samples (8). Wang et al. reported the presence of endplate lesions (Schmorl's nodes, fracture, erosion, or calcification) was associated with frequent back pain (odds ratio (OR) = 2.57) as well as large

endplate lesions, which were associated to a higher degree (OR = 17.88). The sample was smaller than in the present study, comprising 69 male subjects drawn from a cadaveric lumbar spine archive. The present study has shown similar results using a much larger population sample, comprising mainly females.

The strong association between TEP score and LDD as both graded by Pfirrmann and 4 sub trait summary score has previously been shown at a cross-sectional level and now in this longitudinal design (13). Our study defines the relationship between endplate defect and other MRI findings of spine degeneration. Endplate change was found to be significantly associated with degenerate change in the disc, assessed by both the Pfirrmann classification and the more sensitive LDD summary scores. These results support the theory that endplate changes drive DD in the upper lumbar levels, as previously suggested (13). We have identified a significant difference between baseline endplate defect and the development of DD, and the reverse is seen at upper lumbar levels. A significant difference between individuals with and without baseline LDD and prevalence of new MC at follow-up was also observed at all lumbar levels. These results suggest that LDD is followed by MC in some people. According to the endplate vs annulus-driven DD, herniation could cause MC more frequently in lower lumbar levels, even when DD is not severe. This could lead to structural change and progressive LDD. Our findings are strictly only applicable to females, but there is little evidence to suggest that male spines differ in respect of the proposed pathological sequence.

Endplate defect has been identified as an independent risk factor for LDD and MC progression in a clinical sample (19). A TEP score of ≥ 4 was associated with DD at year 4 of follow up in 90 patients with LBP. Progression of LDD was significantly associated with

progression or occurrence of new MC and increasing TEP score. MC was reported to occur last in the development of segmental intervertebral LDD (20). Together, this work provides evidence that endplate change precipitates MC. The present study has also shows that endplate change occurs before DD in a small subset of people.

A number of limitations to this study are acknowledged. The sample was composed primarily of females and very few males. However previously held sex difference in DD has been questioned recently among researchers and most studies are biased towards men so the female predominance in this sample is advantageous. Questionnaire self-assessment was used to define lifetime history of LBP in the twins, therefore whether an individual reports a lifetime history of LBP may be influenced by their current condition. Those individuals presently affected may be more likely to report a history of disabling LBP compared to those who are fit and healthy. One major limitation of the study is that MRI at baseline and follow-up was performed using different equipment and field strengths, which was unavoidable. Use of a MRI scanner with a higher magnetic field strength at follow-up resulted in higher resolution images than those at baseline. This may have an effect on endplate defect coding. Additionally, if defects are small, they may be present and remain undetected at baseline but detected at follow-up due to higher resolution imaging. That said, there are few longitudinal studies available to study the course of spine degeneration and few offer this generous sample size in an unselected population sample. TwinsUK participants have been shown to be representative of singletons for a wide range of lifestyle and demographic traits (10). A relevant strength is the thorough training phase undergone by the evaluators leading to almost perfect inter-rater agreement for endplate defect. Also, in order to provide strong and reliable data, DD was assessed by

two different grading scales (4-point grading scale and Pfirrmann). The confidence intervals for heritability estimation of the sample were small.

CONCLUSION

In summary, the proposed sequence of pathological changes in the general population is that endplate defect triggers DD, which is then followed by MC in some people. A defective endplate is thought to hinder subsequent transport of nutrients to the relatively avascular cells of the intervertebral disc leading to DD. An MRI characteristic of DD is reduced disc height. Coupled with a defective endplate, axial forces and mechanical instability could cause increase likelihood of damage to the vertebral body resulting in the bone marrow oedema characteristic of MC. While this is evident in our population sample, the same may not be true in clinical studies, as people presenting to clinical services may differ in a number of important respects. However, this is the first study to report an estimated heritability (55.3%) for endplate defect, an MR trait only recently explored, which may yet provide the critical link between the various triggers of overall degeneration of the spine.

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Table 1: Baseline characteristics of twins having spine MR scans

Trait	MZ	DZ	Total
	(n = 333)	(n = 663)	(n = 996)
Age, years mean (SD)	55.5 (8.07)	52.6 (7.99)	53.6 (8.13)
Age, years range	31.9-73.8	19.0-72.3	19.0-73.8
Female, %	98.6	94.5	96.1
Disabling back pain duration > 1month, %	26.5	22.2	23.4
BMI, kg/m ² mean (range)	24.5 (16.5-40.7)	25.2 (16.2-51.4)	25.0 (16.2-51.4)

Legend to Table 1

MZ = monozygotic; DZ = dizygotic; n = number; BL = baseline; FU = follow-up; SD = standard deviation; BMI = body mass index; kg = kilograms; m = metres

Table 2: Risk factors for episodes of severe and disabling LBP (n = 820)

Factor	L1/L2, <i>p</i>	L2/L3, <i>p</i>	L3/L4, <i>p</i>	L4/L5, <i>p</i>	L5/S1, <i>p</i>
	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)

Vertebral endplate defect heritability

TEP	0.359	0.00	0.280	0.01	0.351	0.00	0.617	2.5e-	0.671	1.2e-
score	(0.113)	1	(0.112)	3	(0.114)	2	(0.131)	6	(0.127)	7
Age	5.1E-5	0.01	-0.002	0.89	-0.006	0.69	-0.012	0.44	-0.004	0.77
	(0.015)	0	(0.015)	9	(0.015)	1	(0.156)	2	(0.015)	8
Sex	-0.192	0.77	-0.016	0.80	-0.173	0.79	-0.260	0.71	-0.392	0.57
	(0.685)	9	(0.680)	9	(0.669)	5	(0.711)	4	(0.700)	5
BMI	0.055	0.02	0.053	0.02	0.051	0.02	0.050	0.04	0.053	0.03
	(0.024)	0	(0.024)	4	(0.023)	9	(0.025)	1	(0.024)	0

Legend to Table 2

Association was assessed using generalised linear mixed models, adjusting for family structure. BMI = body mass index, SE = standard error, TEP score = total endplate score at baseline, p = p-value

Table 3: Summary table of all association testing for all possible pairwise relationships of, endplate defect, disc degeneration and Modic change

Follow-up trait	Lumbar level	Baseline Trait		
		DD	TEPS	MC
DD	L1-2	-	$p = 0.001$	$p = 0.999$
	L2-3	-	$p = 0.024$	-
	L3-4	-	$p = 0.359$	$p = 0.388$
	L4-5	-	$p = 0.169$	$p = 0.539$
	L5-S1	-	$p = 0.017$	$p = 0.027$
TEPS	L1-2	$p = 0.001$	-	-
	L2-3	$p = 7.0e-05$	-	$p = 0.969$
	L3-4	$p = 0.011$	-	-
	L4-5	$p = 2.5e-06$	-	$p = 0.980$
	L5-S1	$p = 8.1e-05$	-	$p = 0.997$
MC	L1-2	$p = 4.7e-06$	-	-
	L2-3	$p = 0.001$	$p = 0.162$	-
	L3-4	$p = 0.807$	$p = 1.000$	-
	L4-5	$p = 0.090$	$p = 0.004$	-
	L5-S1	$p = 4.4e-05$	$p = 0.002$	-

Legend to Table 3

DD = disc degeneration, MC = Modic change, TEPS = total endplate score, p = p-value

